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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,935	12/21/2000	Timothy Raymond Hirst	9274	8699

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EXAMINER	
HINES, JANA A	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,935	HIRST ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-37* is/are pending in the application.

4a) Of the above claim(s) *6-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/02; 2/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 27, 2005 has been entered.

Amendment Entry

2. The amendments entered January 27, 2005 and January 31, 2005 have been entered. The examiner acknowledges the amendments to the specification. Claim 1 has been amended. Claim 2 has been cancelled. Claims 6-37 have been withdrawn from consideration. Claims 1 and 3-5 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn:

a) The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Holmgren et al., (US Patent 5,681,571) has been withdrawn in light of applicants' amendments; and

b) The rejection of claims 1 and 3-5 under 35 U.S.C. 103(a) as being obvious over Clements (US Patent 6,413,523) in view of Marcello et al., (PNAS 1994) has been in light of applicants' amendments.

Response to Arguments

4. Applicants' arguments with respect to claims 1 and 3-5 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Objection

Drawings

5. The drawings are objected to because the specification only describes Figure 5 however the drawing sheets have Figure 5 A and 5B. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional réplacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must

be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

6. The disclosure is objected to because of the following informality: Page 33, line 35 refers to "plycoprotein" instead of "glycoprotein". Appropriate correction is required.

Claim Objections

7. Claim 1 is objected to because of the following informalities: The claim states "E. Coli." therefore appropriate correction to "*Escherichia coli*" is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The phrase "enhancing the level of an immune response" in claim 1 is a relative; more specifically the term "enhancing" renders the claim indefinite. The phrase "enhancing the level of an immune response" is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree of enhancement. One of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Moreover, there is no disclosure of what the baseline level of an immune response should be which in-turn allows one to know when an enhanced level is reached. Thus the metes and bounds of the phrase cannot be ascertained and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention with respect to this enhanced level of an immune response. Clarification is required to overcome the rejection.

b) Claim 1 recites the limitation "the B subunit" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

c) Claims 1 and 4 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms like *E.coli* in claim 1 and acronyms like HSV-1, HSV-2, EBV, VZV, CMV, HHV-6, HHV-7 and HHV-8 in claim 4 must be spelled out when used for the first time in a chain of claims.

d) Dependant claims 3-5 refer to "A method according to claim...", however the suggested claim language uses the article "The." Thus the suggested claim language is "The method according to claim...".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al., (WO 97/02045) published January 23, 1997. The claim is drawn to a method for enhancing the level of an immune response to a vaccine against an infectious agent in a mammalian subject comprising administering to the subject an effective amount of the B subunit of *Escherichia coli* heat labile enterotoxin (ExtB) wherein the EtxB is free from whole toxin and not linked to an antigen.

Williams et al., teach therapeutic agents for use in the treatment of mammalian diseases (page 1, line 35 – page 2, line 2). The basis of the invention is that the pure B-subunit of *E.coli* heat labile enterotoxin (ExtB) binds to receptors found on the surface of mammalian cells and this binding induces differential immune response effects on lymphocytes including activation of B cells (page 2, lines 1-5). The acronym ExtB means the pure B subunit of *E.coli*

heat labile enterotoxin (page 1, lines 34-36). The ExtB has already been suggested as a vaccine carrier because of its ability to modulate lymphocyte populations (page 10, lines 9-13). Williams et al., teach that the wild type and mutant forms of ExtB have binding capabilities and are known immunomodulators (page 11, line 31- page 12, line 5). Williams et al., teach the administration of EtxB or ExtB mutants to mice (page 14, lines 25-27). The results were expressed as mean IgG and IgA antibody titers in serum, wherein the results indicated an enhanced immune response by the antibodies, see Figure 2. Figure 3 teaches the kinetics of lymphocyte proliferation where the mice were injected with 30ug of a mutant version of ExtB (page 14, line 35- page 15 line 10). The injected amounts of ExtB are effective to enhance the level of the immune response, just as required by the claims. Figure 4 teaches that immunization with either 80ug/ml or 40ug/ml of pure or mutated ExtB caused increased activation of B cells. Therefore Williams et al., teach administering to the subject an effective amount of the ExtB wherein the ExtB is free from whole toxin and not linked to an antigen.

The term "immune response" is not defined by the instant specification, the examiner has defined the term based upon the definition provided by the *Illustrated Dictionary of Immunology* edited by Julius M. Cruse et al., which states that an immune response is known to be the reaction of the animal body to challenge by an immunogen that can be expressed as antibody production. B cells are a class of lymphocytes which upon activation will produce antibodies. Moreover, the instant specification discloses increased IgG and/or IgA

responses, see the instant specification at example 1 (pages 33-34), example 3 (page 35), and example 5 (pages 35-36) which show that these same antibodies have enhanced activity, thus an increase in antibody production is sufficient to meet the limitation of an enhanced immune response. Therefore the increased response of the IgG and IgA antibodies and increased B cell activation as taught by Williams et al., are encompassed within the meaning of enhanced immune response.

Accordingly, Williams et al., clearly teach a method for enhancing the level of an immune response to a vaccine against an infectious agent in a mammalian subject comprising administering to the subject an effective amount of the B subunit of *E.coli* heat labile enterotoxin (ExtB) wherein the EtxB is free from whole toxin and not linked to an antigen just as required by the instant claims.

10. Claims 1 and 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hazama et al., (Immunology, 1993). Claim 1 is drawn to a method for enhancing the level of an immune response to a vaccine against an infectious agent in a mammalian subject comprising administering to the subject an effective amount of the B subunit of *Escherichia coli* heat labile enterotoxin (ExtB) wherein the EtxB is free from whole toxin and not linked to an antigen. The dependant claims are drawn to the vaccine being one for an infectious agent that is a member of the herpes virus family and selected from the group consisting of at least Herpes Simplex Virus –1 (HSV-1).

Hazama et al., teach that the non-toxic B subunit (LTB) of the heat labile toxin produced by enterotoxigenic *Escherichia coli* has been expected to potentiate local IgA antibody response to co-administered foreign antigens (page 643 para. 2). The LTB of Hazama et al., is same B subunit of the heat labile *Escherichia coli* enterotoxin referred to by the instant claims as ExtB. In this study Hazama et al., created a recombinant LTB and investigated the mouse mucosal and systemic immune response elicited by intranasal immunization with several forms of a recombinant viral antigen (page 644, para. 2). These immunizations included truncated Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (t-gD) being co-administered with LTB (page 644, para. 2). Therefore Hazama et al., teach administering to the mammalian mouse subject an effective amount of the LTB wherein the LTB is free from whole toxin and not linked to an antigen, just as required by the claims. Hazama et al., also teach the measurement of the antibody response, see Table 1 (page 646), which shows the administration of effective amounts of LTB alone and the co-administration of t-gD and LTB. Thus the injected amounts of LTB are at an amount effective to enhance the level of an immune response, just as required by the claims. The LTB by itself exhibited high immunogenicity when intranasally administered (page 647, para. 2). Table 2, at page 646, shows protection against a HSV-1 challenge in mice while table 4 shows protective immunity against HSV systemic infection in mice. The glycoproteins of HSV are vaccines against HSV-1 infectious agents, see the instant specification at example 1 (pages 33-34),

example 4 (page 35), and example 7 (pages 36-37) which teach that these same HSV-1 glycoproteins are vaccines against HSV infections.

Therefore Hazama et al., teach a method for enhancing the level of an immune response to a glycoprotein vaccine against a HSV-1 infectious agent in a mouse subject comprising administering to the subject an effective amount of the B subunit of *E.coli* heat labile enterotoxin (ExtB) as known as LTB wherein the EtxB or LTB is free from whole toxin and not linked to an antigen just as required by the instant claims.

Conclusion

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
April 21, 2005